Remarks

I. Information Disclosure Statement

A Supplemental Information Disclosure statement was filed by Applicants on May 1, 2003. Applicants request that the Examiner initial and return the PTO 1449 forms submitted with the Supplemental Information Disclosure Statement with the next Office Action.

II. Summary of Claim Amendments

Applicants have amended Claim 1 to incorporate the limitation of Claim 3 that the transfected cells are seeded onto a biocompatible matrix to form a tissue engineered construct. Applicants have also amended Claims 1 and 18 to indicate that the biocompatible matrix is coated with a material that promotes adhesion of cells. Support for this amendment can be found on page 6, lines 3-5 and on page 11, lines 16-23 of the specification.

III. New Claims 43-52

New Claims 43-44 are directed to a tissue engineered construct that comprises a chondrocyte transfected with a gene for insulin-like growth factor I and a biocompatible matrix. New Claims 45-47 are directed to a method of assembling a tissue engineered construct comprising transfecting a plurality of chodrocytes with a gene for insulin-like growth factor I. Support for Claims 43-47 can be found in the Example section, page 14-20 of the specification which discloses a method of transfecting chondrocytes with a gene for insulin-like growth factor I.

New Claims 48-49 are directed to a tissue engineered construct comprising a mammalian cell transfected with a growth factor, wherein the mammalian cell is a hepatocyte, Islet cell, or endothelial cell. New Claims 50-52 are directed to a method of assembling a tissue engineered construct comprising the step of transfecting a plurality of mammalian cells with a gene for a growth factor, wherein the cells are hepatocytes, Islet cells or endothelial cells. Support for Claims 48-52 can be found on page 6, lines 21-23 of the specification.

IV. Objection to Claim 1

The Examiner objects to Claim 1 because it does not have a period at the end of the claim.

Applicants have amended Claim 1 to correct the typographical error by adding a period at the end of the claim.

V. Rejection of Claims 1-8, 12, 13, 18, and 19 Under 35 U.S.C. § 102(b) Over Sittinger, *et al.*, U.S. Patent No. 5,932,459 (Hereinafter "'459")

A. Summary of the Examiner's Rejection

The Examiner states that '459 teaches a method in which human cells are genetically manipulated to comprise specific genes, such as TGF-β, and are seeded onto an extracellular matrix that may include polymers such as α-hydroxy acids and polylysine.

B. Summary of Applicants' Invention

Applicants claim a tissue engineered construct (Claim 18, as amended, and new Claims 43-44 and 48-49) and a method of assembling the same (Claim 1, as amended, and new Claims 45-47 and 50-52). The tissue engineered construct comprises mammalian cells, such as chondrocytes, that have been transfected with a gene for a growth factor, such as insulin-like growth factor-1 (IGF-1). The cells are seeded onto a biocompatible matrix or implanted into a mammal. In one embodiment, the cells are seeded onto a biocompatible matrix that has been coated with a material that promotes cell adhesion.

C. Summary of '459

'459 discloses a method of making a crosslinkable artificial tissue for transplantation which involves transfecting cells from a particular tissue with a gene for an immunosuppressive factor or a cell-differentiation factor ('459, Col. 2, lines 21-26). '459 does not disclose that cells may be transfected with the gene for insulin-like growth factor-1 (IGF-1) and, in particular, does not disclose that chondrocytes may be transfection with IGF-1 and used to prepare artificial cartilage tissue. In addition, '459 does not disclose transfecting hepatocytes, Islet cells, or endothelial cells with a growth factor to prepare a tissue engineered construct. The genetically

altered cells are suspended in a polymerizable solution containing a polymerizable polypeptide, such as fibrinogen ('459, Col. 4, lines 12-15), or a polymerizable polysaccharide and solidified into a 3-dimensional structure by using thrombin or factors that induce polymerization ('459, Col. 3, line 66 to Col. 4, line 3). The polymerizable solution may also contain absorbable polymer fleece made of polylactide or polyglycolide ('459, Col. 6, lines 8-11). The cells produce a new extracellular matrix (ECM) ('459, Col. 4, lines 3-5).

D. Claims 1-8, 12, 13, 18, and 19

The method of making an artificial tissue for transplantation disclosed in '459 differs from Applicants' method of forming a tissue engineered construct in at least two ways. Unlike Applicants' method, the method of '459 does not involve seeding genetically engineered cells onto a matrix. Instead, the cells are suspended in solution and the entire solution is polymerized to form a matrix that has cells embedded in the polymer structure of the matrix. In addition, because the method of '459 does not include a solid matrix onto which cells can be seeded, the method of '459 and the artificial tissue for transplantation prepared using the disclosed method do not include a matrix that has been coated with a material that promotes cell adhesion.

The standard set forth by the Court of Appeals for the Federal Circuit for anticipation is as follows:

> A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987)

Since Applicants' tissue engineered construct, and method of making the same, include a biocompatible matrix that is coated with a material that promotes cell adhesion, '459 does not discloses all of the elements of Claim 1 or 18, as amended. Therefore, Claims 1 and 18, and the claims depending therefrom, are not anticipated by '459, and Applicants respectfully request that the rejection be reconsidered and withdrawn.

E. New Claims 43-47

New Claims 43-47 are not anticipated by '459 because '459 does not disclose that cells, and in particular chondrocytes, may be transfected with insulin-like growth factor-1 (IGF-1) and used to prepare artificial cartilage tissue for transplantation. Since '459 does not disclose all of the limitations of Claims 43-47, the claims are not anticipated by '459.

F. New Claims 48-52

New Claims 48-52 are not anticipated by '459 because '459 does not disclose that hepatocytes, Islet cells or endothelial cells can be transfected with a gene for a growth factor and used to prepare a tissue engineered construct. Since '459 does not disclose all of the limitations of Claims 48-52, the claims are not anticipated by '459.

VI. Rejection of Claims 1-21 Under 35 U.S.C. § 102(e) Over Breitbart, *et al.*, U.S. Patent No. 6,077,987 (Hereinafter "'987")

A. Summary of the Examiner's Rejection

The Examiner states that '987 discloses a method of making a tissue construct comprising cells that are transformed with a growth factor, wherein the cells synthesize extracellular membrane components and are seeded onto a biocompatible matrix comprising a synthetic or non-synthetic material. The Examiner states that '987 discloses the use of collagen as a cell attachment facilitator.

B. Summary of '987

'987 discloses a method of enhancing and/or increasing the efficiency of tissue repair, particularly bone and cartilage repair, using genetically engineered cells ('987, Col. 3, lines 32-34). The method involves transfecting isolated cells with a gene encoding a growth factor for the particular cell type to be repaired ('987. Col. 3, lines 34-37). When cartilage is to be repaired, the isolated cells may be chondrocytes or fibroblasts ('987, Col. 4, lines 36-37). For cartilage repair, '987 discloses that chondrocytes may be transfected with cartilage growth factor genes, such as transforming growth factor-β 1 (TGF-β1) or cartilage growth factor (CGF) ('987, Col. 7, lines 9-13). '987 does not disclose that chondrocytes may be transfected with insulin-like

growth factor-1 (IGF-1) and use to repair cartilage. The transfected cells may be seeded onto a matrix for implantation to repair a defect and may be cultured on the matrix prior to implantation ('987, Col. 8, lines 35-38). The matrix material may be a synthetic, biocompatible and/or biodegradable polymer ('987, Col. 8, lines 39-42), such as PLA, PGA or PLGA ('987, Col. 8, lines 62-65), or a natural polymer, such as collagen ('987, Col. 9, lines 10-14). '987 does not disclose that hepatocytes, Islet cells or endothelial cells may be transfected with a gene for a growth factor.

C. Claims 1-21

The method of enhancing and/or increasing the efficiency of tissue repair disclosed in '987, and the implants prepared therefrom, differ from Applicants' claimed tissue engineered construct, and method of making the same, because the method and implant of '987 do not include a matrix that has been coated with a material that promotes cell adhesion. Although '987 does disclose that the matrix can be formed from a natural polymer, such as collagen, '987 does not disclose that a matrix can be coated with collagen. The term "coating" indicates that the matrix is covered in a layer of a material that promotes cell adhesion and does not mean that the matrix is formed from the material. Since '987 does not disclose all of the limitations of Claim 1 or 18, it does not anticipate Claims 1 and 18, and the claims depending therefrom. Therefore, Applicants respectfully request that the rejection be reconsidered and withdrawn.

D. New Claims 43-47

New Claims 43-47 are not anticipated by '987 because '987 does not disclose that chondrocytes may be transfected with insulin-like growth factor-1 (IGF-1) and used to prepare artificial cartilage tissue for transplantation. Instead, '987 teaches that chondrocytes should be transfected with transforming growth factor-β 1 (TGF-β1) or cartilage growth factor (CGF). Since '987 does not disclose all of the limitations of Claims 43-47, the claims are not anticipated by '987.

E. New Claims 48-52

New Claims 48-52 are not anticipated by '987 because '987 does not disclose that hepatocytes, Islet cells, or endothelial cells may be transfected with a growth factor and used to

prepare tissue engineered constructs. Since '987 does not disclose all of the limitations of Claims 48-52, the claims are not anticipated by '987.

VII. Rejection of Claim 10 Under 35 U.S.C. § 112, Second Paragraph

The Examiner states that absent some definition or guidance from the specification, the phrase "cell attachment facilitator" is vague and indefinite.

Applicants have amended Claim 10 such that it no longer includes the phrase "cell attachment facilitator," thus obviating the rejection.

SUMMARY

In view of the above amendments and remarks, Applicants respectfully submit that all of the claims are in condition for allowance. Should the Examiner have any questions after reviewing this paper, the Examiner is invited to contact the undersigned at 617-248-5083.

Respectfully submitted,

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